The effects of ginger supplementation on markers of inflammatory and oxidative stress: a systematic review and meta-analysis of clinical trials

Article (Accepted Version)

The effects of ginger supplementation on markers of inflammatory and oxidative stress : A systematic review and meta-analysis of clinical trials

Mohammad Jalali[1,2], Marzieh Mahmoodi[1], Seyedeh Parisa Moosavian[3,2], Ronak Jalali[4], Gordon Ferns[5], Mohammad Hadi Imanieh[6], Abdolhamid Mosallanezhad[7], Zahra Mosallanezhad[2*]

[1] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.

[2] Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

[3] Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[4] Student Research Committee, Golestan University of Medical Sciences, Gorgan, Iran.

[5] Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex, UK

[6] Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

[7] Khalili Educational and Treatment Center, Shiraz University of Medical Sciences, Shiraz, Iran

***Corresponding author:**

Zahra Mosallanezhad,

Nutrition Research Center,

School of Nutrition and Food Sciences,

Shiraz University of Medical Sciences,

Razi Ave, Shiraz, Iran.

Post Code:7153675541,

Tel: +98 7137251005,

Fax: +98 37257288

E-mail: zahra.mosallanj@gmail.com

Abstract

The present systematic review and meta-analysis was conducted to investigate the effects of ginger supplementation on markers of inflammatory and oxidative stress. PubMed, Embase, Scopus and Web of Science were systematically searched to identify relevant clinical trials evaluating the effects of ginger on serum CRP (C-reactive protein), TNF-α (tumor necrosis factor-alpha), IL-6 (interleukin-6), PGE2 (Prostaglandin E2), TAC (Total antioxidant capacity) and MDA (Malondialdehyde) from inception up to September 2019. Mean difference (MD) and its 95 % confidence interval (CI) was determined using a random effects model. Potential publication bias was assessed using visual inspection of funnel plot and Egger's weighted regression tests. After excluding irrelevant records, 20 full-text articles that included 25 separate studies were included to the meta-analysis. Pooled results of the present study indicated a statistically significant effect of ginger on serum CRP, TNF-α, IL-6, TAC and MDA levels following ginger supplementation. Also, the effects of ginger on serum PGE2 was marginally significant. Moreover, the significant heterogeneity disappeared in subgroup analysis performed by age, duration, dosage, and quality. This current analysis indicates that ginger supplementation has significant effects on serum inflammatory markers.

Keywords: ginger, zingiber, inflammation, stress oxidative, meta-analysis

1 Introduction

Low grade systematic inflammation is a complex response that plays an important role in numerous conditions, that include: metabolic syndrome (Safranow et al., 2016), cardiovascular disease (CVD) (Guarner & Rubio-Ruiz, 2015), type 2 diabetes (Donath, 2019), lung diseases (Di

Rosanna & Salvatore, 2012) and different types of cancer (Grivennikov, Greten, & Karin, 2010). C-reactive protein (CRP) is an acute phase protein secreted by the liver in response to other pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) released by macrophages and lymphocyte (Gabay, 2006; Pepys & Hirschfield, 2003). Overproduction of TNF-α and IL-6 contributes to effects on skeletal muscle and adipose tissue (Stanley et al., 2011). Prostaglandin E2 (PGE2) is a potent inflammatory mediator produced from arachidonic acid (AA) by cyclooxygenase 2 (COX2) (Harizi, Corcuff, & Gualde, 2008). A growing body of evidence suggests that PGE2 is involved in the progression of acute and chronic inflammation and autoimmune diseases (Tsuge, Inazumi, Shimamoto, & Sugimoto, 2019). In addition, elevated markers of oxidative stress, that may result from increasing reactive oxygen species and free radicals have been suggested to be involved in the etiology of several chronic diseases (Daenen et al., 2019; Liguori et al., 2018).

Dietary interventions, particularly those that are plant based, have been proposed as alternative treatments to improve low-grade inflammation and oxidative stress (Arabzadegan et al., 2019; Pastori et al., 2015). Ginger has been used both as a food and as an herbal medicine for thousands of years. Ginger is the root of Zingiber officinal, and it contains several compounds such as gingerol, zingerone, shogaol, paradols, and β-bisabolene (Sahebkar, 2011). Studies have shown that ginger possesses antioxidant, antihypertensive, cardioprotective, antidiabetic, antimicrobial, gastroprotective, anticancer, chemopreventive health benefits (Ali, Blunden, Tanira, & Nemmar, 2008; Baliga et al., 2011). In addition, consumption of ginger appears to modulate inflammatory responses, which may result from inhibition of the activity of COX enzymes, and block the production of interleukins, and TNF-a in activated macrophages (Kafeshani, 2015; Liguori et al., 2018).

In several randomized controlled trials (RCTs), ginger supplementation has been shown to affect biomarkers of inflammation and oxidative stress (Kulkarni & Deshpande, 2016; Naderi, Mozaffari-Khosravi, Dehghan, Nadjarzadeh, & Huseini, 2016; Zehsaz, Farhangi, & Mirheidari, 2014; Zick et al., 2015). However, these findings are inconsistent, other studies have not found significant effects of ginger on oxidative stress and inflammatory biomarkers (Azimi, Ghiasvand, Feizi, Hariri, & Abbasi, 2014; Imani et al., 2015). These inconsistencies could be the result of small sample size and varied quality of the studies. It is expected that the ginger supplementation could have beneficial effects on some biomarkers of inflammation and oxidative stress. Therefore, we conducted a meta-analysis to obtain a pooled estimate of the effect of ginger supplementation on biomarkers of inflammation and oxidative stress in clinical trials, and also to assess whether an administration of ginger could ameliorate antioxidant and inflammation status.

2 Method

The present meta-analysis was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 Data sources and search strategy

Online databases (PubMed, Embase, Scopus and Web of Science) were systematically searched by two independent reviewers (MJ and ZM) to find related papers that assessed the effects of ginger supplementation on improvement of inflammatory and oxidative stress markers from incent up to 18 September 2019, without any restriction on the language and time of publication. The following search terms were used in titles and abstracts: (ginger OR zingiber OR “Zingiber officinale” OR “zingiberene” OR “β-bisabolene” OR “α-farnesene” OR “β-sesquiphellandrene” OR “α-curcumene”) AND ("inflammation" OR "inflamma*" OR "inflammatory" OR IL-6 OR

interleukin-6 OR “interleukin 6” OR interleukin6 OR IL6 OR “IL 6” OR "CRP" OR “hs-CRP” OR "C-reactive protein" OR “TNF-α” OR “TNFα” OR “TNF α” OR “tumor necrosis factor-α” OR “tumor necrosis factor α” OR “tumor necrosis factor α” OR “tumor necrosis factor alpha” OR “TNF-alpha” OR "PGE*" OR "prostaglandin" OR “MDA” OR “Malondialdehyde” OR “TAC” OR “Total antioxidant capacity”) AND ("trial" OR "randomi*" OR "control" OR "clinical" OR "intervention" OR "randomized" OR "placebo" OR "blind" OR "supplement*"). Furthermore, the wild-card term “*” was used to increase the sensitivity of the search strategy. EndNote X9 was used to moderate the literature screening and duplicates finding. Also, hand searching was done using the list of references, Google Scholar and Cochrane Library.

2.2 Inclusion and Exclusion criteria

Studies were included that met the following characteristics: (1) a clinical trial with any kind of design, (2) using ginger without no other nutrients as a supplement in adults (> 18 years old), (3) reporting a change of at least one of outcomes including CRP, TNF-α, IL-6, PGE2, TAC or MDA and (4) having more than 10 days’ intervention duration. Non-English language trials, animal studies and papers which their data were not convertible were excluded.

2.3 Data selection

After deletion of duplicate records, two authors (MJ and ZM) independently reviewed the remained studies to determine their suitability for inclusion. Screening process was performed in two stages. At first, title/abstract of articles were scanned, publications that were irrelevant were excluded. Then, the remaining articles were evaluated for eligibility using full text in the second stage. the following data were extracted using pre-defined list including the first authors’ last name, location of trial, sample size, age, dosage of ginger, type of supplement, duration of the

intervention, and quality of the included articles by AM and RJ, independently. Any doubts were resolved by MJ.

2.4 Quality evaluation

The Jadad scale with a maximum of 5 points (randomization: 2, blinding: 2 and dropouts descriptive: 1) was used to assess the quality of the trials. Trials scoring <3 were considered as low quality studies and the rest as high quality (Clark et al., 1999).

2.5 Statistical analysis

Stata V13 was used to analyze all data. Forest plot, in which results from individual trials were displayed as a square and a horizontal line, representing the ginger effect estimate together with its 95% confidence interval. The meta-analyses measure of effect and its confidence interval were represented by a diamond and the lateral points, respectively. In case of heterogeneity, fixed or random effects models were executed to calculate mean difference (MD) and its 95% confidence interval (CI). A significant and high heterogeneity was assessed using p value < 0.05 and $I^2 \geq 50\%$, respectively. Moreover, subgroup analysis was done by age, dosage, intervention duration and quality. Net changes in outcomes were calculated by subtracting the value at baseline from that after intervention in the active-treated groups and in the control ones. SDs of the mean difference were obtained as the following procedure: SD = square root $[((\text{SD pre})^2 + (\text{SD post})^2) - (2r \times \text{SD pre} \times \text{SD post})]$, considering a correlation coefficient (r) = 0.5 for both pre-tests / post-tests. In case of those studies that reported standard error (SE), SD was obtained using this formula: $(\text{SD} = \text{SE} \times \sqrt{n})$. Sensitivity analysis was performed to find the effect of each study on the pooled result. Publication bias was examined using Egger's regression test, and

visual inspection of funnel plot when the number of studies was more than 10. A p value < 0.05 was considered as statistically significant.

3 Results

3.1 Data selection

The flowchart of data selection process is presented in Figure 1. At first, 1128 records were identified using the strategy search of online databases (PubMed, Embase, Scopus and Web of Sciences). After finding duplicates, 529 references were screened by title and abstract. At the next step, 469 records were excluded and 60 full-text articles were assessed for eligibility. Finally, 20 articles considering 25 separate studies with different characteristics were included in this meta-analysis (Arablou et al., 2014; Atashak, Peeri, Azarbayjani, Stannard, & Haghighi, 2011; Ayaz & Roshan, 2012; Azimi et al., 2014; Black, Herring, Hurley, & O'Connor, 2010; Di Rosanna & Salvatore, 2012; Grivennikov et al., 2010; Guarner & Rubio-Ruiz, 2015; Hunninghake et al., 1984; Imani et al., 2015; Kulkarni & Deshpande, 2016; Kumar, Singh, Saxena, & Saxena, 2013; Mahluji, Ostadrahimi, Mobasseri, Ebrahimzade Attari, & Payahoo, 2013; Mozaffari-Khosravi, Naderi, Dehghan, Nadjarzadeh, & Fallah Huseini, 2016; Naderi et al., 2016; Rahimlou, Yari, Hekmatdoost, Alavian, & Keshavarz, 2016; Safranow et al., 2016; Vahdat Shariatpanahi et al., 2013; Zehsaz et al., 2014; Zick et al., 2015).

3.2 Trial characteristics:

Characteristics of included clinical trials are shown in Table 1. These studies were published from 2010 to 2016. Of these 19 studies, 4 were conducted in the USA (Black et al., 2010; Zehsaz et al., 2014; Zick et al., 2015), 13 in Iran (Arablou et al., 2014; Atashak et al., 2011; Ayaz & Roshan, 2012; Azimi et al., 2014; Di Rosanna & Salvatore, 2012; Grivennikov et al., 2010;

Guarner & Rubio-Ruiz, 2015; Hunninghake et al., 1984; Imani et al., 2015; Mahluji et al., 2013; Mozaffari-Khosravi et al., 2016; Naderi et al., 2016; Rahimlou et al., 2016; Safranow et al., 2016; Vahdat Shariatpanahi et al., 2013), and 2 in India (Kulkarni & Deshpande, 2016; Kumar et al., 2013). Overall, 446 and 442 subjects participated in the intervention and control groups, respectively. The participants' age range was between 20-58 years old and also the range of intervention duration was between 10 days to 3 months. The minimum and maximum dosage were 0.12 g/day and 3 g/day of ginger, respectively. Four of the included studies were considered as low quality (Ayaz & Roshan, 2012; Kulkarni & Deshpande, 2016; Kumar et al., 2013; Safranow et al., 2016) and the other 15 were considered as high quality ones (Arablou et al., 2014; Atashak et al., 2011; Azimi et al., 2014; Black et al., 2010; Di Rosanna & Salvatore, 2012; Grivennikov et al., 2010; Guarner & Rubio-Ruiz, 2015; Hunninghake et al., 1984; Imani et al., 2015; Kulkarni & Deshpande, 2016; Mahluji et al., 2013; Mozaffari-Khosravi et al., 2016; Naderi et al., 2016; Rahimlou et al., 2016; Vahdat Shariatpanahi et al., 2013; Zehsaz et al., 2014; Zick et al., 2015).

3.3 The effect of ginger supplementation on inflammatory markers:

As indicated in Figure 2A, the meta-analysis on 285 subjects in the intervention group and 280 subjects in the control group showed a significant reduction in serum CRP after ginger supplementation (MD = -1.032, 95% CI = [-1.533, -0.531], $P < 0.0001$) with a high heterogeneity among the included studies ($I^2 = 86.0\%$, $P < 0.0001$). The significant heterogeneity disappeared in the subgroup analysis: age (less than 30 years, 30-40 years and more than 50 years), doses up to 1 g/d and quality (low quality). No potential publication bias (Figure 5) was found ($P = 0.635$).

The forest plot of 7 effect sizes (Figure 2B) showed a significant change in serum TNF-α after ginger supplementation as compared with the control group (MD = -0.950, 95% CI = [-1.588, -0.312], P = 0.004) with a significant heterogeneity among the studies (I^2 = 88.1%, P < 0.0001). Based on the subgroup analysis, heterogeneity was reduced in duration (up to one month). No significant publication bias was identified (P = 0.197).

The pooled effect estimate of 5 datasets (Figure 2C) indicated a significant reduction in serum IL-6 following ginger supplementation in comparison with the control group (MD = -1.025, 95% CI = [-1.710, -0.339], P = 0.003). A significant heterogeneity was observed in this meta-analysis (I^2 = 72.8%, P = 0.005). In subgroup analysis, a reduction of heterogeneity was found for age (40 – 50 years). No evidence of a significant publication bias was found (P = 0.274).

This meta-analysis (Figure 2D) showed that ginger supplementation had a marginally significant effect on serum PGE2 as compared to the control group (MD = -0.316, 95% CI = [-0.632, -0.000], P = 0.050). No evidence of a high heterogeneity was found among the included effect sizes (I^2 = 0.0%, P = 0.475).

3.4 The effect of ginger supplementation on stress oxidative:

The pooled effect estimate of 5 datasets (Figure 3A) showed a significant change of serum TAC following ginger supplementation as compared to the control group (MD = 0.933, 95% CI = [0.652, 1.334], P < 0.0001). A high degree of heterogeneity was observed among studies in the overall effects (I^2 = 95.2%, P < 0.0001). Evidence of a significant publication bias was not found (P = 0.760).

The forest plot of 7 effect sizes (Figure 3B) indicated a significant reduction of serum MDA after ginger supplementation as compared to the control group (MD = -0.652, 95% CI = [-1.278, -

0.027], P = 0.041). A high degree of overall heterogeneity (I^2 = 82.7%, P < 0.0001) was reduced in the subgroup analysis that was performed by duration of exposure (10 weeks), dosage (Less than 1.5 g/day) and quality (Low quality) of the trials. No significant publication bias was found in this meta-analysis (P = 0.168).

3.5 Sensitivity analysis:

Results of sensitivity analyses showed that removal of none of the studies could affect the significance of pooled results (Figure 4).

4 Discussion

The present systematic review and meta-analysis assessed the influence of ginger supplementation on serum CRP, TNF-α, PGE2, IL-6, TAC and MDA concentrations from available RCTs. The meta-analysis of data from nineteen RCTs revealed a significant effect of ginger supplementation on plasma CRP, TNF-α, PGE2 and IL-6 concentrations. However, a significant reduction was observed in the circulating CRP and TNF-α at doses 2-3 g/day and 1-2 g/day, respectively. This means that the higher dosage of ginger supplementation had a potential effect on lowering plasma inflammatory cytokines. The anti-inflammatory effect of ginger has been investigated in previous studies (Arablou et al., 2014; Kim, Chun, Kundu, & Surh, 2004). However, these findings are inconsistent. The variability of results in these studies may be attributed to the differences in study design, quality of studies, supplemental duration, individual characteristics, and ginger dose. NF-kβ is the key regulator of the inflammatory process. It has been shown that NF-kβ activates the expression of inflammatory target genes, including genes encoding cytokines, chemokines, and the enzyme cyclooxygenase 2 (COX2). Among them, COX2 leads to the formation of prostaglandins in response to inflammation and enhanced the

production of pro-inflammatory cytokines. Several studies have shown that ginger has a potential anti-inflammatory activity and inhibited inflammatory response by suppression of the NF-kβ activation, thereby it could reduce the expression of cytokine genes (TNF- and IL-6) (Wang, Ke, Bao, Hu, & Chen, 2017). The TNF-α lowering effect of ginger has been shown in some studies; this is consistent with our findings (Luettig et al., 2016; Sherif, Abas, Zaitoun, & Technology, 2018) A recent meta-analysis has reported that acute-phase proteins including CRP were also suppressed in this process (Mazidi, Gao, Rezaie, & Ferns, 2016). Naderi et al. showed that ginger powder supplementation at a dose of 1 g/d for 12-week decreased inflammatory markers, that included serum CRP in patients with knee osteoarthritis (Naderi et al., 2016), which is consistent with the results of a study by Rahimlou et al. (Rahimlou et al., 2016). Moreover, the other anti-inflammatory effects of ginger are caused by its inhibitory effect on COX-2 and lipoxygenase, thereby suppressing arachidonic acid metabolism. Therefore, it reduced platelet aggregation, formation of pro-inflammatory thromboxane, and prostaglandin. It was shown that ginger had anti-inflammatory effects through inhibition of prostaglandin synthesis (Azimi et al., 2014). The study carried out by Phan et al. showed that ginger inhibited the formation of nitric oxide and inflammatory cytokines, the enzyme prostaglandin synthase; therefore, it could decrease inflammation (Phan et al., 2005). In an animal study by Thomson et al., it was also demonstrated that consumption of 500 mg/kg ginger for 4 weeks decreased serum prostaglandin E2 through the inhibitory effect of ginger on prostaglandin (Thomson et al., 2002).

Several compounds in ginger are responsible for serotonin blocker which is related to the reduction of TNFα, IL1β, IL6, IL2, and prostaglandins (Aryaeian & Tavakkoli, 2015). Some studies also indicated the effects of ginger supplementation on inflammatory cytokines. In agreement with our findings, 500mg of ginger powder resulted in the reduction of plasma IL-1β,

IL-6, and TNF-α in male endurance runners who had consumed 500 mg of ginger powder (Mao et al., 2019). Several other studies have also demonstrated this beneficial effect (Azimi et al., 2014; Mashhadi et al., 2013; Suk et al., 2017).

Moreover, our subgroup analysis showed that ginger supplementation had a lowering effect o serum TNF-α and CRP in interventions with a duration 2-3 months. Thus, a higher efficacy of supplementation was observed in trials with higher duration than shorter duration.

The pooled effect of several studies also showed a significant mean difference for the serum levels of TAC and MDA. It has been shown that ginger had potential antioxidant properties due to high amount of phenolic compounds (Attia, Ibrahim, Nabil, & Aziz, 2013). Ginger supplementation potentiates the antioxidant defense system through the activation of nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) and the expression of several antioxidant enzymes and thereby could reduce the generation of ROS and lipid peroxidation. Therefore, it protected against oxidative stress and prevented the depletion of antioxidants (Al Hroob, Abukhalil, Alghonmeen, & Mahmoud, 2018; Mao et al., 2019) which lead to markedly lower MDA concentration (Attia et al., 2013).

This is the first systematic review and meta-analysis to investigate the effect of ginger supplementation on inflammatory and oxidative stress biomarkers. However, two limitations of our study should be noted. First, in most of the studies included, findings were not adjusted for potential confounders, which could potentially influence results. Second, subjects in these studies had a diverse set of health conditions. Moreover, ginger is a popular spice with negligible side effects and most of the references have reported no side effect of ginger consumption (Black et al., 2010; Imani et al., 2015; Shidfar et al., 2015; Zick et al., 2015), however, few studies have

demonstrated that some anti-inflammatory compounds of ginger (gingerdiones and shogoals) have fewer adverse effect (Mahluji et al., 2013; Zehsaz et al., 2014).

5 Conclusion

Ginger supplementation may improve the anti-inflammatory and antioxidant status. However, further large well-designed studies are warranted to support the finding.

6 Funding

This work was prepared without the aid of any specific funding.

7 Conflict of interest

The authors declare no conflict of interest.

8 Footnotes

MD = mean difference

SD = standard deviation

CI = confidence interval

CRP = C-reactive protein

TNF-α = tumor necrosis factor-alpha

IL = interleukin

PGE2 = Prostaglandin E2

TAC = total antioxidant capacity

MDA = Malondialdehyde

References

Al Hroob, A. M., Abukhalil, M. H., Alghonmeen, R. D., & Mahmoud, A. M. (2018). Ginger alleviates hyperglycemia-induced oxidative stress, inflammation and apoptosis and protects rats against diabetic nephropathy. *Biomedicine & Pharmacotherapy, 106*, 381-389.

Ali, B. H., Blunden, G., Tanira, M. O., & Nemmar, A. (2008). Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. *Food and chemical Toxicology, 46*(2), 409-420.

Arablou, T., Aryaeian, N., Valizadeh, M., Sharifi, F., Hosseini, A., & Djalali, M. (2014). The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. *Int J Food Sci Nutr, 65*(4), 515-520. doi:10.3109/09637486.2014.880671

Arabzadegan, N., Daneshzad, E., Fatahi, S., Moosavian, S. P., Surkan, P. J., & Azadbakht, L. (2019). Effects of dietary whole grain, fruit, and vegetables on weight and inflammatory biomarkers in overweight and obese women. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity*, 1-9.

Aryaeian, N., & Tavakkoli, H. (2015). Ginger and its effects on inflammatory diseases. *Adv Food Technol Nutr Sci Open J, 1*(4), 97-101.

Atashak, S., Peeri, M., Azarbayjani, M. A., Stannard, S. R., & Haghighi, M. M. (2011). Obesity-related cardiovascular risk factors after long- term resistance training and ginger supplementation. *J Sports Sci Med, 10*(4), 685-691.

Attia, A. M., Ibrahim, F. A., Nabil, G. M., & Aziz, S. W. (2013). Antioxidant effects of whole ginger (Zingiber officinale Roscoe) against lead acetate-induced hematotoxicity in rats. *Journal of Medicinal Plants Research, 7*(17), 1108-1113.

Ayaz, A., & Roshan, V. D. (2012). Effects of 6-weeks water-based intermittent exercise with and without Zingiber officinale on pro-inflammatory markers and blood lipids in overweight women with breast cancer. *Journal of Applied Pharmaceutical Science, 2*(5), 218-224. doi:10.7324/JAPS.2012.2547

Azimi, P., Ghiasvand, R., Feizi, A., Hariri, M., & Abbasi, B. (2014). Effects of Cinnamon, Cardamom, Saffron, and Ginger Consumption on Markers of Glycemic Control, Lipid Profile, Oxidative Stress, and Inflammation in Type 2 Diabetes Patients. *Rev Diabet Stud, 11*(3-4), 258-266. doi:10.1900/rds.2014.11.258

Baliga, M. S., Haniadka, R., Pereira, M. M., D'Souza, J. J., Pallaty, P. L., Bhat, H. P., & Popuri, S. (2011). Update on the chemopreventive effects of ginger and its phytochemicals. *Critical reviews in food science and nutrition, 51*(6), 499-523.

Black, C. D., Herring, M. P., Hurley, D. J., & O'Connor, P. J. (2010). Ginger (Zingiber officinale) reduces muscle pain caused by eccentric exercise. *J Pain, 11*(9), 894-903. doi:10.1016/j.jpain.2009.12.013

Clark, H. D., Wells, G. A., Huët, C., McAlister, F. A., Salmi, L. R., Fergusson, D., & Laupacis, A. J. C. c. t. (1999). Assessing the quality of randomized trials: reliability of the Jadad scale. *20*(5), 448-452.

Daenen, K., Andries, A., Mekahli, D., Van Schepdael, A., Jouret, F., & Bammens, B. (2019). Oxidative stress in chronic kidney disease. *Pediatric Nephrology, 34*(6), 975-991.

Di Rosanna, P., & Salvatore, C. (2012). Reactive oxygen species, inflammation, and lung diseases. *Current pharmaceutical design, 18*(26), 3889-3900.

Donath, M. Y. (2019). *Inflammation and type 2 diabetes: from basic science to treatment.* Paper presented at the Seminars in immunopathology.

Gabay, C. (2006). Interleukin-6 and chronic inflammation. *Arthritis research & therapy, 8*(2), S3.

Grivennikov, S. I., Greten, F. R., & Karin, M. (2010). Immunity, inflammation, and cancer. *Cell, 140*(6), 883-899.

Guarner, V., & Rubio-Ruiz, M. E. (2015). Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. In *Aging and Health-A Systems Biology Perspective* (Vol. 40, pp. 99-106): Karger Publishers.

Harizi, H., Corcuff, J.-B., & Gualde, N. (2008). Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology. *Trends in molecular medicine, 14*(10), 461-469.

Hunninghake, G. W., Garrett, K. C., Richerson, H. B., Fantone, J. C., Ward, P. A., Rennard, S. I., . . . Crystal, R. G. (1984). Pathogenesis of the granulomatous lung diseases. *American Review of Respiratory Disease, 130*(3), 476-477.

Imani, H., Tabibi, H., Najafi, I., Atabak, S., Hedayati, M., & Rahmani, L. J. N. (2015). Effects of ginger on serum glucose, advanced glycation end products, and inflammation in peritoneal dialysis patients. *31*(5), 703-707.

Kafeshani, M. (2015). Ginger, micro-inflammation and kidney disease. *Nutrition, 31*, 703-707.

Kim, S. O., Chun, K. S., Kundu, J. K., & Surh, Y. J. (2004). Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-κB and p38 MAPK in mouse skin. *Biofactors, 21*(1-4), 27-31.

Kulkarni, R. A., & Deshpande, A. R. (2016). Anti-inflammatory and antioxidant effect of ginger in tuberculosis. *J Complement Integr Med, 13*(2), 201-206. doi:10.1515/jcim-2015-0032

Kumar, S., Singh, U., Saxena, K., & Saxena, R. J. I. J. H. M. (2013). Supplementation of ginger with anti-tuberculosis treatment (ATT): A better approach to treat anemic pulmonary tuberculosis patients. *1*, 17-20.

Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., . . . Bonaduce, D. (2018). Oxidative stress, aging, and diseases. *Clinical interventions in aging, 13*, 757.

Luettig, J., Rosenthal, R., Lee, I. F. M., Krug, S. M., Schulzke, J. D. J. M. n., & research, f. (2016). The ginger component 6-shogaol prevents TNF-α-induced barrier loss via inhibition of PI3K/Akt and NF-κB signaling. *60*(12), 2576-2586.

Mahluji, S., Ostadrahimi, A., Mobasseri, M., Ebrahimzade Attari, V., & Payahoo, L. (2013). Anti-inflammatory effects of zingiber officinale in type 2 diabetic patients. *Adv Pharm Bull, 3*(2), 273-276. doi:10.5681/apb.2013.044

Mao, Q.-Q., Xu, X.-Y., Cao, S.-Y., Gan, R.-Y., Corke, H., & Li, H.-B. (2019). Bioactive compounds and bioactivities of ginger (zingiber officinale roscoe). *Foods, 8*(6), 185.

Mashhadi, N. S., Ghiasvand, R., Askari, G., Hariri, M., Darvishi, L., & Mofid, M. R. J. I. j. o. p. m. (2013). Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. *4*(Suppl 1), S36.

Mazidi, M., Gao, H.-K., Rezaie, P., & Ferns, G. A. (2016). The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. *Food & nutrition research, 60*(1), 32613.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. J. A. o. i. m. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *151*(4), 264-269.

Mozaffari-Khosravi, H., Naderi, Z., Dehghan, A., Nadjarzadeh, A., & Fallah Huseini, H. (2016). Effect of Ginger Supplementation on Proinflammatory Cytokines in Older Patients with Osteoarthritis: Outcomes of a Randomized Controlled Clinical Trial. *J Nutr Gerontol Geriatr, 35*(3), 209-218. doi:10.1080/21551197.2016.1206762

Naderi, Z., Mozaffari-Khosravi, H., Dehghan, A., Nadjarzadeh, A., & Huseini, H. F. (2016). Effect of ginger powder supplementation on nitric oxide and C-reactive protein in elderly knee osteoarthritis patients: A 12-week double-blind randomized placebo-controlled clinical trial. *J Tradit Complement Med, 6*(3), 199-203. doi:10.1016/j.jtcme.2014.12.007

Pastori, D., Carnevale, R., Bartimoccia, S., Nocella, C., Tanzilli, G., Cangemi, R., . . . Pignatelli, P. (2015). Does Mediterranean diet reduce cardiovascular events and oxidative stress in atrial fibrillation? In: Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA.

Pepys, M. B., & Hirschfield, G. M. (2003). C-reactive protein: a critical update. *The Journal of clinical investigation, 111*(12), 1805-1812.

Phan, P. V., Sohrabi, A., Polotsky, A., Hungerford, D. S., Lindmark, L., & Frondoza, C. G. (2005). Ginger extract components suppress induction of chemokine expression in human synoviocytes. *Journal of Alternative & Complementary Medicine, 11*(1), 149-154.

Rahimlou, M., Yari, Z., Hekmatdoost, A., Alavian, S. M., & Keshavarz, S. A. (2016). Ginger Supplementation in Nonalcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Hepat Mon, 16*(1), e34897. doi:10.5812/hepatmon.34897

Safranow, K., Dziedziejko, V., Rzeuski, R., Czyżycka, E., Bukowska, H., Wojtarowicz, A., . . . Ciechanowicz, A. (2016). Inflammation markers are associated with metabolic syndrome and ventricular arrhythmia in patients with coronary artery disease. *Advances in Hygiene & Experimental Medicine/Postepy Higieny i Medycyny Doswiadczalnej, 70*.

Sahebkar, A. (2011). Potential efficacy of ginger as a natural supplement for nonalcoholic fatty liver disease. *World journal of gastroenterology: WJG, 17*(2), 271.

Sherif, M. H., Abas, A.-S. M., Zaitoun, L. A. J. R. J. o. P., & Technology. (2018). Ginger extract protect Iodinated Contrast Media Nephrotoxicity in rats through modulation of Oxidative Stress, Cystain C, NGAL and TNF α. *11*(12), 5439-5448.

Shidfar, F., Rajab, A., Rahideh, T., Khandouzi, N., Hosseini, S., & Shidfar, S. (2015). The effect of ginger (Zingiber officinale) on glycemic markers in patients with type 2 diabetes. *J Complement Integr Med, 12*(2), 165-170. doi:10.1515/jcim-2014-0021

Stanley, T. L., Zanni, M. V., Johnsen, S., Rasheed, S., Makimura, H., Lee, H., . . . Grinspoon, S. K. (2011). TNF-α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *The Journal of Clinical Endocrinology & Metabolism, 96*(1), E146-E150.

Suk, S., Kwon, G. T., Lee, E., Jang, W. J., Yang, H., Kim, J. H., . . . research, f. (2017). Gingerenone A, a polyphenol present in ginger, suppresses obesity and adipose tissue inflammation in high-fat diet-fed mice. *61*(10), 1700139.

Thomson, M., Al-Qattan, K., Al-Sawan, S., Alnaqeeb, M., Khan, I., & Ali, M. (2002). The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent. *Prostaglandins, leukotrienes and essential fatty acids, 67*(6), 475-478.

Tsuge, K., Inazumi, T., Shimamoto, A., & Sugimoto, Y. (2019). Molecular mechanisms underlying prostaglandin E2-exacerbated inflammation and immune diseases. *International immunology, 31*(9), 597-606.

Vahdat Shariatpanahi, Z., Mokhtari, M., Taleban, F. A., Alavi, F., Salehi Surmaghi, M. H., Mehrabi, Y., & Shahbazi, S. (2013). Effect of enteral feeding with ginger extract in acute respiratory distress syndrome. *J Crit Care, 28*(2), 217.e211-216. doi:10.1016/j.jcrc.2012.04.017

Wang, J., Ke, W., Bao, R., Hu, X., & Chen, F. (2017). Beneficial effects of ginger Zingiber officinale Roscoe on obesity and metabolic syndrome: a review. *Annals of the New York Academy of Sciences, 1398*(1), 83-98.

Zehsaz, F., Farhangi, N., & Mirheidari, L. (2014). The effect of Zingiber officinale R. rhizomes (ginger) on plasma pro-inflammatory cytokine levels in well-trained male endurance runners. *Cent Eur J Immunol, 39*(2), 174-180. doi:10.5114/ceji.2014.43719

Zick, S. M., Turgeon, D. K., Ren, J., Ruffin, M. T., Wright, B. D., Sen, A., . . . Brenner, D. E. (2015). Pilot clinical study of the effects of ginger root extract on eicosanoids in colonic mucosa of subjects at increased risk for colorectal cancer. *Mol Carcinog, 54*(9), 908-915. doi:10.1002/mc.22163

Table 1. characteristics of included studies

First author	Publication year	Country	Type of supplement	Participants	Sample size (%male) (Intervention /Control)	Age, mean (SD)	Duration of intervention	Dosage (g/day)	Quality
Black 1	2010	USA	raw	Healthy adults	17 / 17	21.1 (0.7)	11 d	2	High quality
Black 2	2010	USA	heated	Healthy adults	20 / 20	20.6 (0.6)	11 d	2	High quality
Atashak 1	2011	Iran	capsule	Obese men	8 / 8	23.66 (3.39)	10 w	1	High quality
Atashak 2	2011	Iran	capsule	Obese men	8 / 8	23.71 (3.81)	10 w	1	High quality
Ayaz 1	2012	Iran	capsule	Women with breast cancer	10 / 10	46.4 (5.5)	6 w	2.25	Low quality
Ayaz 2	2012	Iran	capsule	Women with breast cancer	10 / 10	47.5 (4.6)	6 w	2.25	Low quality
Kumar	2013	India	capsule	Anemic Pulmonary Tuberculosis patients	36 / 35	20 - 58	4 w	0.5	Low quality
Mahluji	2013	Iran	tablet	Type 2 diabetic patients	26 / 28	49.27 (5.18)	8 w	2	High quality
Vahdat Shariatpanahi	2013	Iran	Enteral	Patients with acute respiratory distress syndrome	16 / 16	41.19 (3.69)	10 d	0.12	High quality

Arablou	2014	Iran	capsule	T2DM patients	33 / 30	52.6 (8.4)	12 w	1.6	High quality
Atashak 1	2014	Iran	Capsule	Obese men	8 / 8	23.66 (3.39)	10 w	1	Low quality
Atashak 2	2014	Iran	Capsule	Obese men	8 / 8	23.71 (3.81)	10 w	1	Low quality
Azimi	2014	Iran	raw-powder	T2DM patients	41 / 39	55.21 (1.1)	8 w	3	High quality
Zehsaz	2014	USA	capsule	Well-trained male endurance runners	14 / 14	23.21 (2.77)	12 w	1.5	High quality
Attari	2015	Iran	Tablet	Obese women	39 / 31	35.25 (7.30)	12 w	2	High quality
Imani	2015	Iran	capsule	Peritoneal dialysis patients	18 / 18	56 (2.5)	10 w	1	High quality
Khandouzi	2015	Iran	Capsule	Type 2 diabetic	22 / 19	45.20 (7.64)	12 w	2	High quality
Shidfar	2015	Iran	capsule	T2DM patients	22 / 23	45.2 (7.64)	12 w	3	High quality
Zick	2015	USA	capsule	Patients who were at increased risk for colorectal cancer	10 / 10	51.1 (11.7)	28 d	2	High quality
Kulkarni	2016	India	powder	Pulmonary TB patients	34 / 35	31.62 (6)	4 w	3	Low quality
Mozaffari-Khosravi	2016	Iran	capsule	Old patients with knee osteoarthritis	50 / 50	57.98 (6.2)	12 w	0.5	High quality
Naderi	2016	Iran	capsule	Old patients with knee osteoarthritis	50 / 50	57.98 (6.2)	12 w	0.5	High quality
Rahimlou	2016	Iran	capsule	Non-alcoholic fatty liver disease patients	23 / 21	45.45 (2.3)	12 w	2	High quality
Nikkhah	2019	Iran	Capsule	Patients with	22 / 24	41.41 (11.4)	12 w	2	High

			ulcerative colitis				quality

SD: standard deviation, W: week, D: day, T2DM: type 2 diabetes mellitus

Table 2. The effect of ginger supplementation on CRP, TNF-α, IL-6 and PGE2 by age, duration, dosage and quality of the studies

	Subgroups		Effect size	95% CI	*P* value	I^2 heterogeneity	*P* value for heterogeneity
CRP	Age	Less than 30 years	2	-2.168, 0.177	0.096	58.1%	0.122
		30 – 40 years	3	-1.632, -0.815	< 0.0001	0.0%	0.502
		40 – 50 years	3	-4.405, -0.021	0.048	96.2%	< 0.0001
		More than 50 years	4	-0.711, 0.001	0.05	53.0%	0.094
	Duration	Up to one month	1	-1.665, -0.657	< 0.0001	-	-
		1 - 2 months	4	-1.271, -0.027	0.041	70.0%	0.018
		2 – 3 months	7	-2.096, -0.436	0.003	90.2%	< 0.0001
	Dosage	Up to 1 g/d	5	-1.231, -0.325	0.001	57.4%	0.052
		1 – 2 g/d	3	-4.018, 0.118	0.065	96.5%	< 0.0001
		2 – 3 g/d	4	-1.606, -0.174	0.015	75.2%	0.007
	Quality	Low quality	3	-1.632, -0.815	< 0.0001	0.0%	0.502
		High quality	9	-1.583, -0.354	0.002	88.6%	< 0.0001
TNF-α	Age	Less than 30 years	1	-1.687, -0.126	0.023	-	-
		30 – 40 years	1	-0.536, 0.409	0.792	-	-
		40 – 50 years	3	-2.948, 0.284	0.106	93.6%	< 0.0001

	Duration	More than 50 years	2	-1.882, -0.075	0.034	86.3%	0.007
		Up to one month	2	-0.548, 0.235	0.433	0.0%	0.490
		1 - 2 months	1	-0.971, 0.110	0.118	-	-
		2 – 3 months	4	-2.447, -0.527	0.002	89.6%	< 0.0001
	Dosage	Up to 1 g/d	2	-1.979, 0.115	0.081	84.%	0.011
		1 – 2 g/d	4	-2.295, -0.175	0.022	90.5%	< 0.0001
		2 – 3 g/d	1	-0.536, 0.409	0.792	-	-
IL-6	Age	Less than 30 years	1	-2.617, -0.860	< 0.0001	-	-
		30 – 40 years	2	-3.120, 0.197	0.084	80.3%	0.024
		40 – 50 years	2	-0.835, 0.021	0.062	0.0%	0.674
		More than 50 years	-	-	-	-	-
	Dosage	Up to 1 g/d	1	-1.233, 0.178	0.143	-	-
		1 – 2 g/d	2	-2.364, 0.378	0.156	85.9%	0.008
		2 – 3 g/d	2	-3.120, 0.197	0.084	80.3%	0.024
	Quality	Low quality	2	-3.120, 0.197	0.084	80.3%	0.024
		High quality	3	-1.575, -0.035	0.040	72.6%	0.026

CRP: C-reactive protein, TNF-α: tumor necrosis factor-alpha, IL-6: interleukin-6, CI: confidence interval

Table 3. The effect of ginger supplementation on TAC and MDA by age, duration, dosage and quality of the studies

	Subgroups		Effect size	95% CI	*P* value	I^2 heterogeneity	*P* value for heterogeneity
TAC	Age	More than 40 years	2	0.255, 1.130	0.002	90.4%	0.001
		Less than 40 years	3	0.915, 2.006	< 0.0001	97.1%	< 0.0001
	Duration	10 weeks	2	-1.437, 0.086	0.082	84.9%	0.010
		12 weeks	3	1.030, 1.793	< 0.0001	96.3%	< 0.0001
	Dosage	Less than 1.5 g/day	2	-1.437, 0.086	0.082	84.9%	0.010
		More than 1.5 g/day	3	1.030, 1.793	< 0.0001	96.3%	< 0.0001
	Quality	Low quality	2	-1.437, 0.086	0.082	84.9%	0.010
		High quality	3	1.030, 1.793	< 0.0001	96.3%	< 0.0001
MDA	Age	More than 40 years	4	-1.505, -0.475	< 0.0001	60.0%	0.057
		Less than 40 years	3	-1.037, 0.758	0.761	72.1%	0.028
	Duration	10 weeks	3	-0.875, 0.091	0.112	0.0%	0.573
		12 weeks	4	-1.783, 0.212	0.123	90.9%	< 0.0001
	Dosage	Less than 1.5 g/day	3	-0.875, 0.091	0.112	0.0%	0.573
		More than	4	-1.783, 0.212	0.123	90.9%	< 0.0001

	Quality	1.5 g/day Low quality	2	-1.317, 0.111	0.098	0.0%	0.483
		High quality	5	-1.465, 0.126	0.099	88.2%	< 0.0001

TAC: total antioxidant capacity, MDA: Malondialdehyde, CI: confidence interval

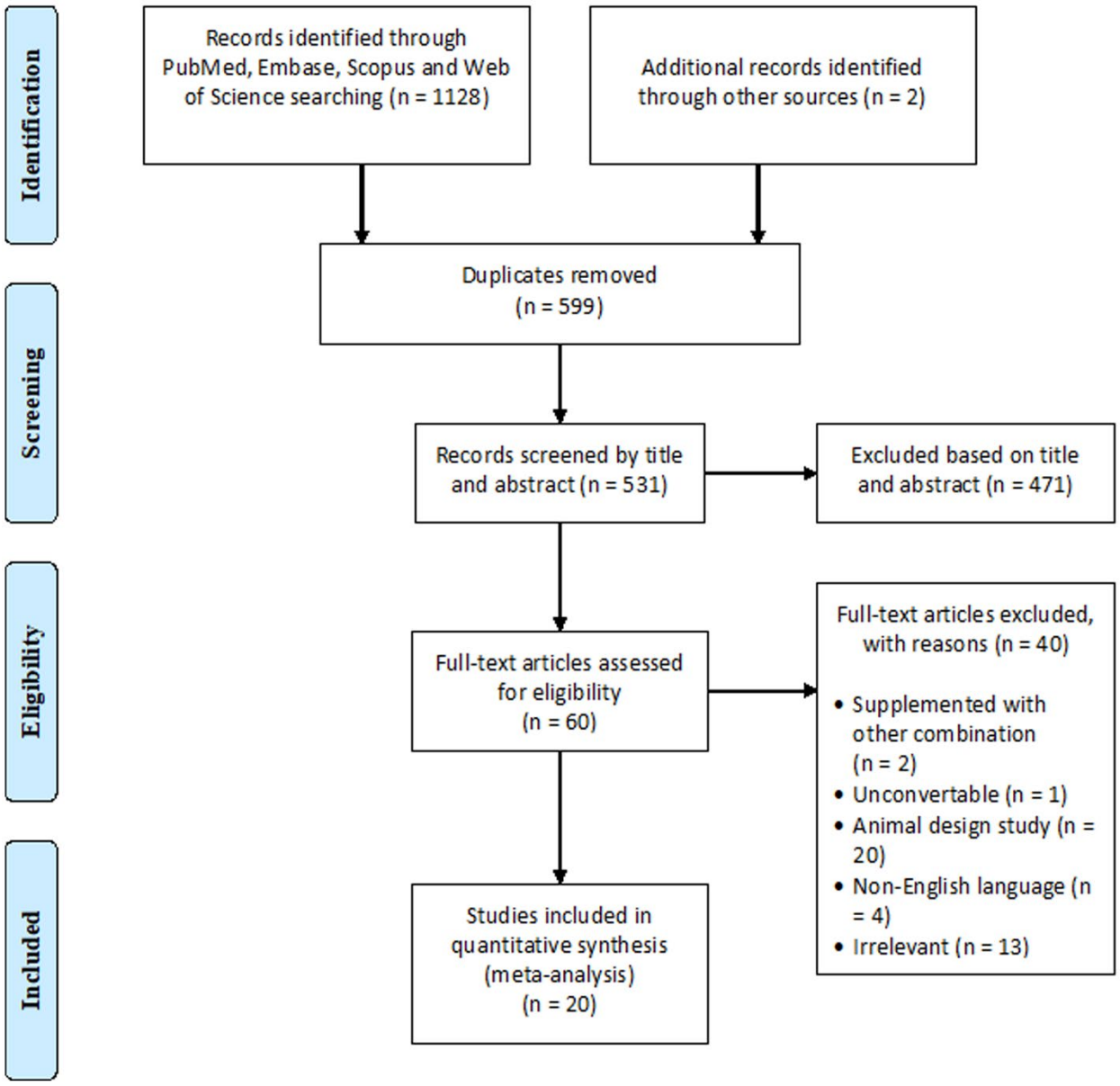

Figure 1. Flow diagram of data selection process

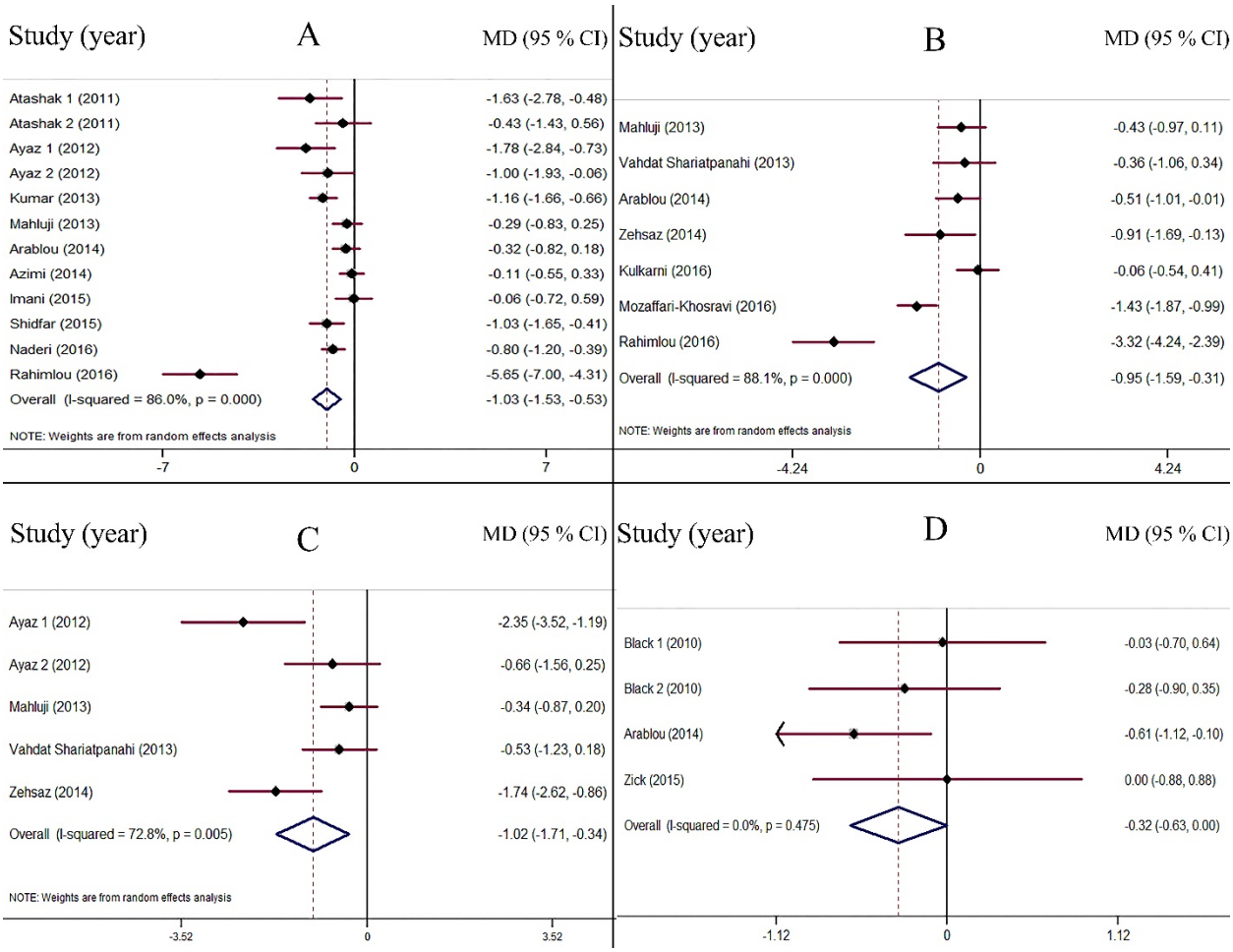

Figure 2. The effect of ginger supplementation on CRP (A), TNF-α (B), IL-6 (C) and PGE2 (D)

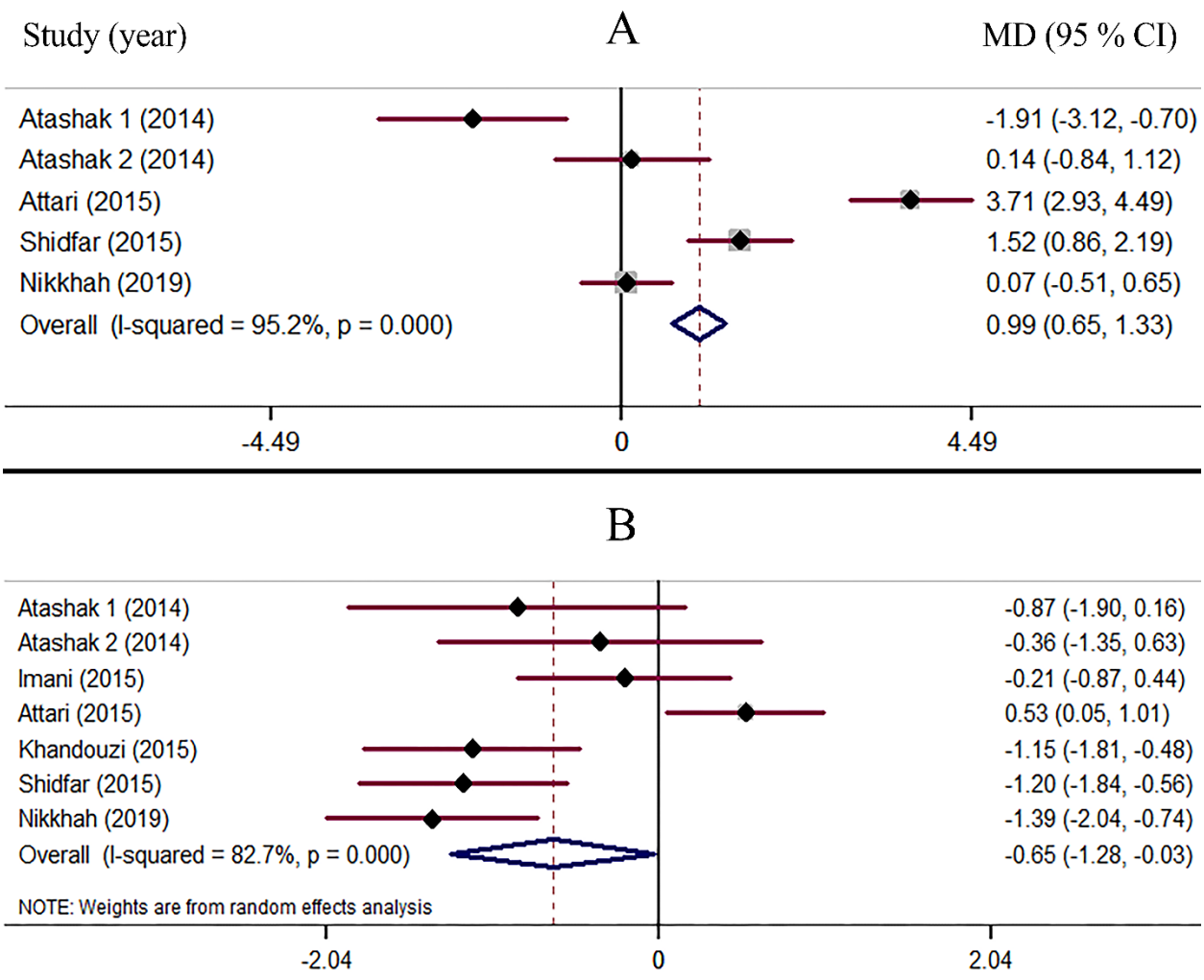

Figure 3. The effect of ginger supplementation on TAC (A) and MDA (B)

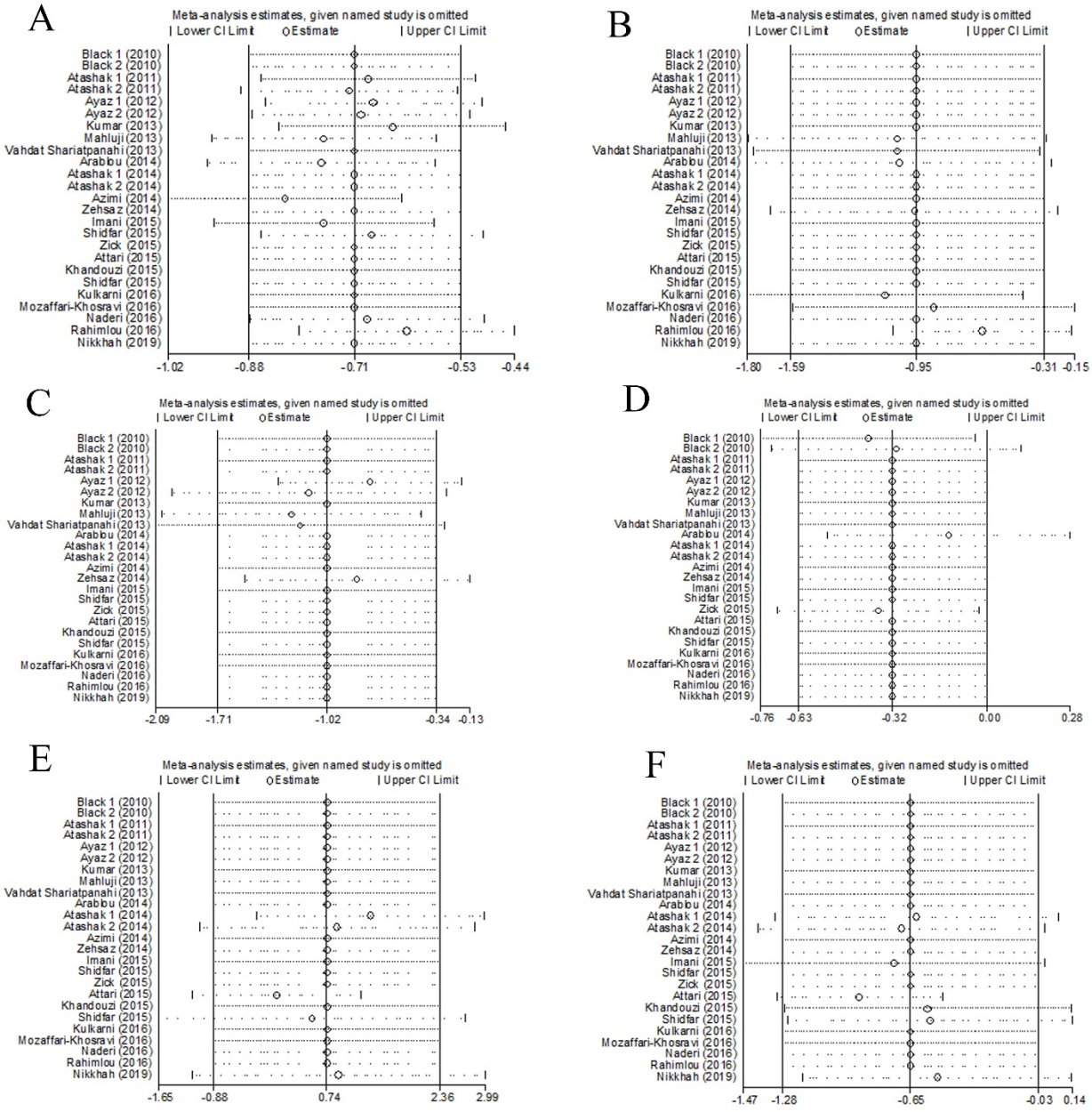

Figure 4. The results of sensitivity analysis of CRP (A), TNF-α (B), IL-6 (C), PGE2 (D), TAC (E) and MDA (F)

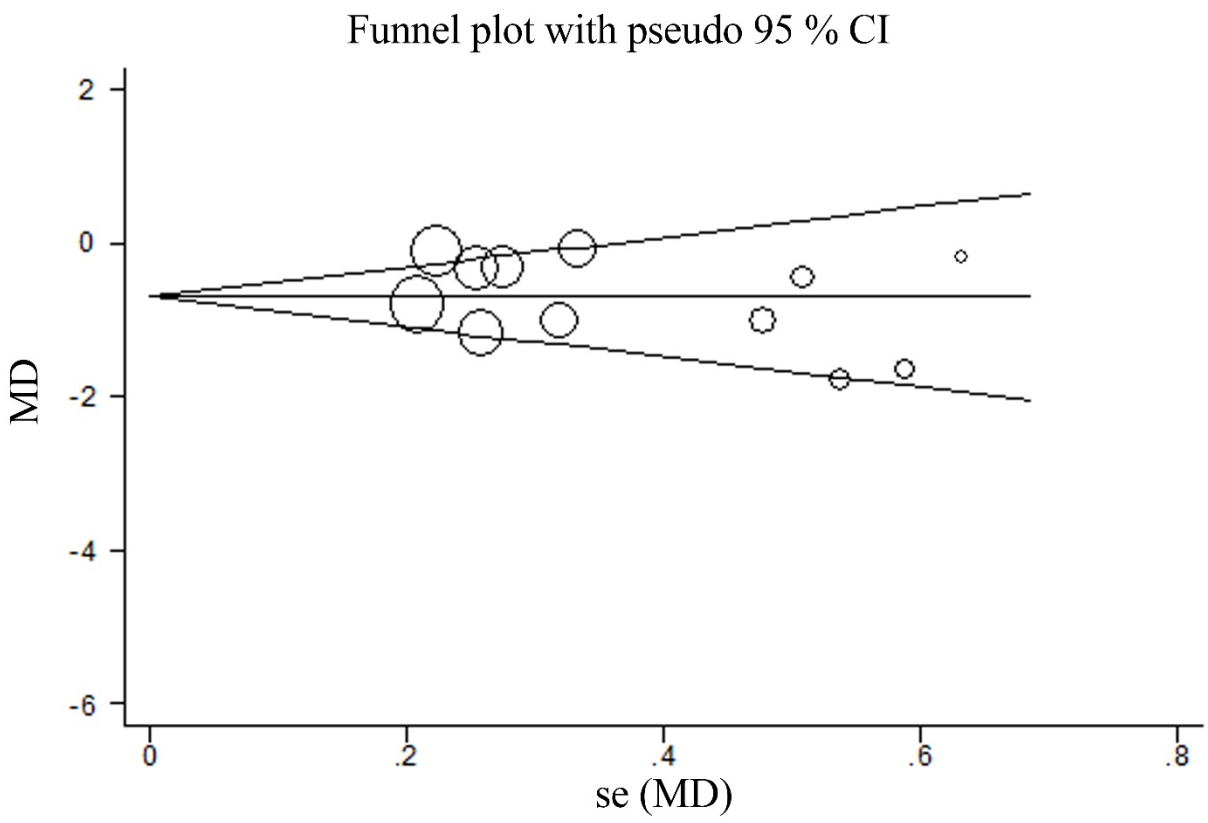

Figure 5. Funnel plot for the efficacy of ginger supplementation on serum CRP levels